

In re Application of:
Yamakawa and Berlin
Application No.: 10/750,515
Filing Date: December 31, 2003
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PATENT
Attorney Docket No. INTEL1140 (P15614)

AMENDMENT TO THE SPECIFICATION

Please amend the specification as follows:

Please replace paragraph [0009]:

"[0009] FIGS. 2A and 2C illustrate barcode patterns for encoding individual nucleotides using gold nanoparticle 30 tags and a DNA backbone. The figure illustrates a 2 nm gold nanoparticle (small circle) and a 10 nm gold nanoparticle (large circle)."

with:

--[0009] FIGS. 2A, 2B, and 2C illustrate barcode patterns for encoding individual nucleotides using gold nanoparticle 30 tags and a DNA backbone. The figure illustrates a 2 nm gold nanoparticle (small circle) and a 10 nm gold nanoparticle (large circle).--

Please replace paragraph [0113]:

"[0113] In certain aspects of the methods of the present invention, the tags on the nanocode include raman tags. Furthermore, these tags can include composite organic-inorganic nanoparticles (See U.S. Ser. No. [], filed Dec. 29, 2003, entitled "Composite Organic-Inorganic Nanoparticles") (referred to herein as COIN nanoparticles or "COINs"). COINs are Raman-active probe constructs that include a core and a surface, wherein the core includes a metallic colloid including a first metal and a Raman-active organic compound. The COINs can further comprise a second metal different from the first metal, wherein the second metal forms a layer overlying the surface of the nanoparticle. The COINs can further comprise an organic layer overlying the metal layer, which organic layer comprises the probe. Suitable probes for attachment to the surface of the SERS-active nanoparticles for this embodiment include, without limitation, antibodies, antigens, polynucleotides, oligonucleotides, receptors, ligands, and the

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like. However, for these embodiments, COINs are typically attached to an oligonucleotide probe."

with:

--[0113] In certain aspects of the methods of the present invention, the tags on the nanocode include raman tags. Furthermore, these tags can include composite organic-inorganic nanoparticles (See U.S. Ser. No. 10/748,336, filed Dec. 29, 2003, entitled "Composite Organic-Inorganic Nanoparticles") (referred to herein as COIN nanoparticles or "COINs"). COINs are Raman-active probe constructs that include a core and a surface, wherein the core includes a metallic colloid including a first metal and a Raman-active organic compound. The COINs can further comprise a second metal different from the first metal, wherein the second metal forms a layer overlying the surface of the nanoparticle. The COINs can further comprise an organic layer overlying the metal layer, which organic layer comprises the probe. Suitable probes for attachment to the surface of the SERS-active nanoparticles for this embodiment include, without limitation, antibodies, antigens, polynucleotides, oligonucleotides, receptors, ligands, and the like. However, for these embodiments, COINs are typically attached to an oligonucleotide probe.--

Please replace paragraph [0183]:

"[0183] Another modality of SPM is atomic force microscopy (AFM). Methods of biomolecule analysis by AFM are generally known in the art (e.g., Uchihashi et al., "Application of Noncontact-Mode Atomic Force Microscopy to Molecular Imaging," <http://www.foresight.org/Conferences/MNT7/Abstracts/Uchihashi>). In AFM microscopy, the probe is attached to a spring-loaded or flexible cantilever that is in contact with the surface to be analyzed. Contact is made within the molecular force range (i.e., within the range of interaction of Van der Waal forces). Within AFM, different modes of operation are possible, including contact mode, non-contact mode and TappingMode™."

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with:

--[0183] Another modality of SPM is atomic force microscopy (AFM). Methods of biomolecule analysis by AFM are generally known in the art (e.g., Uchihashi et al., "Application of Noncontact-Mode Atomic Force Microscopy to Molecular Imaging," which recites, "Observation of organic and biological materials at molecular level has recently attracted wide attention especially in surface science involving biomolecules such as DNA. The most powerful technique that is applicable to insulating materials is atomic force microscopy (AFM). There have been several studies demonstrating the possibility of molecular-level imaging of organic molecules [Meyer et al., Nature (1991) 349:398] and DNA [Hansma et al., Biophys J (1995) 68:1672]. However, the use of the contact or taping mode causes the local deformation of sample surfaces and the damage of the tip apex due to high loading and friction force between the tip and the sample surface. Such damage of both the tip apex and the sample surface prevent us from achieving higher-resolution imaging of molecular structures. Recent progress of AFM in the noncontact mode using the frequency modulation (FM) technique allows us to image various surfaces with true atomic resolution [Sugawara et al Science (1995) 270:1646; Bammerlin et al., Probe Microscopy (1997) 1:3]. This technique can be applied to weakly adsorbed organic and biological molecules on solid surfaces without any damage of both the sample surfaces and the tip apex. In this study, we have applied noncontact-AFM to high resolution imaging of self-assembled films of nucleic acid bases adsorbed on a graphite surface and DNA adsorbed on a mica surface in an ultrahigh vacuum (UHV). The self-assembled films of the nucleic acid bases on graphite substrate were prepared by a molecular beam deposition under UHV condition and were annealed at about 330K to improve their crystallinity. The DNA was deposited on the freshly cleaved mica surface by placing a drop of DNA solution and then the sample was transferred into the UHV chamber. The noncontact-AFM measurement using Si tip was performed under the UHV at room temperature. For the self-assembled films of the nucleic acid bases, we resolved not only the lattice images of molecular packing structures but also individual molecules. Point defect and domain structures were also imaged. The images of individual molecules revealed the fine structures which depended on the molecular structures of nucleic

acid bases. These noncontact-AFM images were clearly different from those obtained by STM reported in previous studies [Freud et al. Phy Rev (1997) 55:5394; Edelwirth et al., Sur Sci (1998) 417:201]. Next we discussed the optimum condition for high resolution imaging by noncontact-mode AFM for the DNA sample. As a result, we found that the removal of the water layer covering on the sample surface by annealing was required for high-resolution imaging.
Moreover, we resolved the right-handed helix turns in B-DNA). In AFM microscopy, the probe is attached to a spring-loaded or flexible cantilever that is in contact with the surface to be analyzed. Contact is made within the molecular force range (i.e., within the range of interaction of Van der Waal forces). Within AFM, different modes of operation are possible, including contact mode, non-contact mode and TappingMode™.--

Please replace paragraph [0187]:

“[0187] Another variation is chemical force microscopy (CFM), in which the probe tip is functionalized with a chemical species and scanned over a sample to detect adhesion forces between the chemical species and the sample (e.g., Frisbie et al., Science 265:2071-2074, 1994). Chemicals with differing affinities for nanocode materials, such as gold or silver, may be incorporated into an AFM probe tip and scanned across a surface to detect and identify nanocodes. Another SPM mode of potential use is force modulation imaging (Maivald et al., Nanotechnology 2:103, 1991). Uchihashi et al. (<http://www.foresight.org/Conferences/MNT7/Abstracts/Uchihashi>) disclose a method of biomolecule imaging using frequency modulation in non-contact mode AFM.”

with:

--[0187] Another variation is chemical force microscopy (CFM), in which the probe tip is functionalized with a chemical species and scanned over a sample to detect adhesion forces between the chemical species and the sample (e.g., Frisbie et al., Science 265:2071-2074, 1994). Chemicals with differing affinities for nanocode materials, such as gold or silver, may be incorporated into an AFM probe tip and scanned across a surface to detect and identify nanocodes. Another SPM mode of potential use is force modulation imaging (Maivald et al.,

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Nanotechnology 2:103, 1991). Uchihashi et al. (“Application of Noncontact-Mode Atomic Force Microscopy to Molecular Imaging”, supra) disclose a method of biomolecule imaging using frequency modulation in non-contact mode AFM.--